REMARKS

Amendments to the Claims

Claims 14-17, and 32-34 are pending. Applicants have corrected the typographical errors identified by the Examiner in claims 14, 32 and 33 of the Amendment filed January 5, 2004, which was not entered. Claims 33 and 34 have been amended. Support for the addition of "over the rate of target cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate" can be found in the specification on pages 5 and 6, as well as page 24, lines 11-22. This amendment does not introduce new matter, but is added solely for purposes of clarification in response to rejections made by the examiner. Applicants believe that it is proper for the present amendment to be entered since it places the application in condition for allowance. Alternatively, entry of this amendment is proper since it places the claims in better form for appeal, does not raise any new issues, and does not require further consideration or search.

Rejection Under 35 U.S.C. § 103

Claims 14-16 and 33 were rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,370,681 to Herweck et. al. ("Herweck") in view of U.S. Patent No. 5,171,264 to Merrill ("Merrill"). Claim 17 was rejected under 35 U.S.C. § 103(a) as obvious over Herweck in view of Merrill, and further in view of U.S. Patent No. 5,522,895 to Mikos *et al.* ("Mikos"). The applicants respectfully traverse these rejections to the extent that it is applied to the claims as amended.

Claim 34 has not been rejected over the prior art.

The claimed invention

Claims 14-17, and 33 define a method for enhanced growth of cells growing eukaryotic cells tethered to a biocompatible substrate with biocompatible polymeric tethers, and growth effector molecules, where the tethers are coupled to the substrate by the same linkers as the tethers are coupled to the growth effector molecules, the tethers prevent the internalization of the growth effector molecules, and the growth effector molecules are present in a concentration effective to enhance the rate of cell growth over the rate of cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate.

Herweck

Herweck discloses implantable devices for sustained release of a bioactive material, such as a therapeutic agent, a cell type, or a diagnostic agent, into a fluid flow pathway of a patient (see column 3, lines 14-16 and 30-37). The surface of the device is first coated or modified with glycoproteins such as fibronectin prior to seeding it with cells (see column 4, lines 62-68). Herweck discloses that such coating may result in improved adhesion of cells (see column 6, lines 23-29). As recognized by the Examiner, Herweck does not disclose or suggest the use of a tether attaching a growth effector molecule to a substrate but merely coats, or adsorbs, the factor upon the substrate. More importantly, Herweck **does not describe or provide the motivation to lead one of ordinary skill in the art to grow cells** by maintaining the cells in contact with the composition defined therein, which comprises a tether attaching a growth effector molecule to a substrate without causing internalization of the effector molecule by the cells. Furthermore, Herweck does not teach that the rate of target cell growth would be enhanced by using tethered

growth effector molecules over simply coating or adsorbing the growth effector molecules to the substrate.

In summary, Herweck does not recognize the critical concentration of growth effector molecules, the need for a tether that allows the growth effector molecules to enhance the rate of growth without internalization of the growth effector molecules, or the role the tethers and linkers play in such a substrate.

Merrill

Merrill discloses star molecules of polyethyleneoxide (PEO) that are biocompatible and demonstrate non-thrombogenic properties. These star molecules could be useful in Applicants' methods, as discussed in the specification at page 7, lines 3-20. Merrill teaches that the star PEO molecules can be attached to an appropriate support surface to reduce thrombosis, to assist in protein purifications, and other proposed activities.

As shown in Figure 4, Merrill describes using PEO molecules as tethers for attaching IgG, which is not a growth effector molecule. In addition, Merrill does not teach the requirement for a critical concentration of growth factors to enhance growth, the requirement for tethers which allow the growth factors to bind to cells but which prevent internalization, or the role linkers play.

The combination of Herweck and Merrill

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, **absent some teaching, suggestion or incentive supporting the combination.** Accordingly, Herweck does not suggest that it would be advantageous to tether growth factors to the substrate, and Merrill does not suggest using the star molecules for

tethering growth effector molecules to a substrate. In addition, the combination of the references does not disclose a growth effector molecule concentration which enhances target cell growth over the rate of target cell growth with soluble growth effector molecules or growth effector molecules adsorbed to a substrate. Furthermore, one skilled in the art would not combine these references and automatically envisage the specific use of covalent tether linkages to prevent growth effector internalization by the cells. Therefore, it is evident that Herweck and Merrill, in combination, do not teach or motivate one of ordinary skill in the art to make and use a composition comprising a growth effector covalently linked through a tether to a substrate surface.

Accordingly, Herweck and Merrill, even if someone were led to combine them, would not lead one of ordinary skill in the art to make and use a composition as defined in the claims for stimulating cell growth; nor would Herweck and Merrill, combined, lead one of ordinary skill in the art to have a reasonable expectation that the claimed method could be used as defined by claim 34. Therefore, claims 14-16, 33 and 34 are not *prima facie* obvious over Herweck in view of Merrill ((*see, Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986); *see also* MPEP § 2141).

Herweck or Merrill in combination with Mikos

Claim 17 was rejected as obvious in view of Herweck in combination with Merrill, and further in view of Mikos. Claim 17 further defines the polymer of claim 16 as biodegradable.

Mikos describes a biodegradable polymeric matrix which can be seeded with cells and implanted. In particular, Mikos describes a biodegradable, bioresorbable, three-dimensional template for repair and replacement of diseased or injured bone (col. 2, lines 10-57).

Mikos discloses biodegradable polymers, but provides no teaching that one should tether growth effector molecules to a biodegradable substrate, only that one should directly absorb cells to a biodegradable substrate. Therefore, Herweck in view of Merrill in combination with Mikos would not make claim 17 obvious. Only with hindsight would one be led to combine Mikos, Merrill and Herweck. There is no teaching that would lead one to the combination. Even in combination, however, the three references do not disclose or make obvious chemically coupling growth effector molecules to a biodegradable substrate in a density and with appropriate linkers to result in the enhanced growth of attached cells over the rate of cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate, without internalization of the molecules. (*see, Hodosh v. Block Drug Co., Inc.*, 786 F.2d at 1143 n.5, 229 USPQ at 187 n.5; *see also* MPEP § 2141).

Double Patenting Rejection

Claims 14-17, and 33 were rejected under the judicially created doctrine of obviousness-type double patenting as obvious over claims 1-4 of U.S. Patent No. 5,906,828 ("the '828 patent") and further in view of U.S. Patent No. 4,954,637 to Nitecki et al. ("Nitecki"), U.S. Patent No. 5,508,164 to Kausch et al., ("Kausch") and the applicants' alleged admissions.

Claims 32 and 34 were rejected under the judicially created doctrine of obviousness-type double patenting over claim 20 of U.S. Patent No. 6,045,818 ("the '818 patent") and further in view of U.S. Patent No. 4,954,637 to Nitecki et al. ("Nitecki"), U.S. Patent No. 5,508,164 to Kausch et al., ("Kausch") and the applicants' alleged admissions. Applicants respectfully traverse the rejections.

The proper test in this case is not a one-way test for obviousness as proposed by the examiner, but a two way test. Federal Circuit decisions have confirmed that a "two-way" rather than a "one-way" patentability test applies when an inventor or assignee files a patent application claiming an improvement or combination invention *after* a patent application claiming the basic or subcombination invention, but the *second-filed application issues first* through no inventor or assignee fault. See re Braat, 937 F.2d 589, 19 USP Q2d 1289 (Fed. Cir. 1991). This application was filed prior to the '828 patent, but was subject to an administrative delay on the part of the PTO during the appeal process. Where a two-way obviousness determination is required, it is necessary to apply the Graham obviousness analysis twice, once with the application claims as the claims in issue, and once with the patent claims as the claims in issue. In this situation, an obvious-type double patenting rejection is appropriate **only** where each analysis compels a conclusion that the invention defined in the claims in issue is an obvious variation of the invention defined in a claim in the other application/patent.

If a two-way test for obviousness is applied, it is clear that the claims of the '828 patent and the claims of the current application are not obvious variations of each other.

Claims 1-4 of the '828 patent define a method of growing eukaryotic cells:

1. A method for growing eukaryotic cells comprising

(a) bringing into contact the cells and a composition comprising

a biocompatible solid substrate,

biocompatible branched water soluble polymeric tethers, and

growth effector molecules,

wherein one end of each tether is covalently linked to the substrate, each tether is able to covalently link more than one growth effector molecule, each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, and

the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth over the rate of target cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate, without internalization of the molecules; and

(b) maintaining the contacting cells and composition under conditions and for a time sufficient to cause the cells to grow;

wherein the step of bringing into contact comprises administering the composition to a patient in need of cell growth.

Claims 2-4 further define the route of administration of the composition and the shape and biodegradability of the substrate in the method of claim 1.

First, an analysis must be performed with the application claims as the claims in issue. Claims 14-17 and 33 do not require administration of cells to a patient. There is nothing within claims 14-17 and 33 which would lead one skilled in the art to believe the subject matter is a

therapeutic. Only the claims may be considered in a double patenting rejection - no reference back to the specification or other materials to support the rejection. There is nothing that would lead one skilled in the art to look at claims 14-17 and 33, and suggest the additional step of administering the composition to a patient, as defined by the claims of the '828 patent.

Therefore, claims 14-17 and 33 are not obvious from the claims of the'828 patent when the claimed invention is considered as a whole.

Next, one must perform an analysis with the patent claims as the claims in issue. Claim 1 of the '828 patent stipulates that each tether is branched and able to covalently link more than one growth effector molecule. These claim limitations are not found in claim 33 of the present application, nor are they found in claims 14-17. Thus, claims 1-4 of the '828 patent are not *prima facie* obvious over claims 14-17, and 33.

Claims 32 and 34 are drawn to a method for screening for a compound for an effect on tissue comprising bringing into contact the compound to be tested and a composition comprising

a biocompatible solid substrate,

biocompatible, polymeric tethers,

growth effector molecules, and

growing cells,

wherein one end of each tether is covalently linked to the substrate and one end is covalently linked to a growth effector molecule so that the growth effector molecule cannot be internalized by cells attached to the substrate;

wherein the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth over the rate of target cell growth with soluble

growth effector molecules and growth effector molecules adsorbed to a substrate, without internalization of the molecules;

wherein the tether is covalently linked to the substrate and to the growth effector molecule by the same attachment agents; and

wherein the growing cells are bound to the growth effector molecules; incubating the compound and the composition under conditions promoting cell growth; and observing the cells for any effect not observed in cells not brought into contact with the composition.

Claim 20 of the '818 patent defines a method of testing a compound for an effect on tissue, as follows:

20. A method of testing a compound for an effect on tissue comprising

(a) bringing into contact the compound to be tested and a composition comprising

a biocompatible solid substrate,

biocompatible branched water soluble polymeric tethers comprising a polymeric material selected from the group consisting of polyethylene oxide, polyvinyl alcohol, polyhydroxyalkyl (meth)acrylate, polyacrylamide, and starches,

growth effector molecules, and

growing cells,

wherein one end of each tether is covalently linked to the substrate, each tether is able to covalently link more than one growth effector molecule, each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth over the rate of

target cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate, without internalization of the molecules, and

wherein the growing cells are bound to the growth effector molecules;

(b) incubating the compound and the composition under conditions promoting cell growth; and

(c) observing the cells for any effect not observed in cells not brought into contact with the composition,

wherein the substrate is selected from the group consisting of glasses, metals, polystyrenes, polyethylene vinyl acetates, polypropylenes, polymethacrylates, polyacrylates, polyethylenes, polyethylene oxides, polysilicates, polycarbonates, polytetrafluoroethylene, fluorocarbons, nylon, silicon rubber, polyanhydrides, polyglycolic acids, polyhydroxyacids, polyesters, polycapralactone, polyhydroxybutyrate, polyphosphazenes, polyorthoesters, polyurethanes, and combinations thereof .

Like claim 1 of the '828 patent, claim 20 of the '818 patent stipulates that each tether is branched and able to covalently link more than one growth factor molecule. However, these claim limitations are not found in claim 34 of the present application, nor are they found in claim 32. Therefore, claim 20 is not *prima facie* obvious over claims 32 and 34.

There is nothing in claims 32 and 43 that would lead one skilled in the art to substitute branched tethers for tethers as currently defined. Absent some teaching, claims 32 and 34 cannot be obvious over the claims in the '818 patent.

Applying the two-way obviousness test demonstrates that neither the claims in issue nor the claims in the '828 patent or the '818 patent are obvious variations of each other. Therefore the obviousness-type double patenting rejection is improper.

U.S.S.N. 08/398,555
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AMENDMENT AND RESPONSE TO OFFICE ACTION

Allowance of claims 14-17 and 32-34, as amended, is respectfully solicited.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that the enclosed Response to Office Action and all documents shown as being attached is being facsimile transmitted to Mail Stop Non-Fee Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Date: February 5, 2004

Peggy Bailey

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